REMARKS

Claim Amendments

Claims 1-33 are pending. Claims 3, 13, 14, 26-30, 32 and 33 stand withdrawn. Applicants have amended claims 1, 2 and 17 to delete the reference to "a nucleic acid that inhibits the production of Cip/Kip family protein." This subject matter relates to Groups II and IV as set forth in the Restriction Requirement mailed on December 29, 2006. Applicants also amended claim 1 to recite "*in vitro*" in response to the Office Action's requirement that the claims be amended to recite the elected subject matter (i.e., *in vitro* methods). Applicants reserve their right to pursue the non-elected subject matter in one or more continuation and/or divisional applications. Claims 4, 11 and 18 have been amended to delete the recitation of "capable." No new matter has been added.

Objections

The Office Action objects to claims 1, 4-12, 15 and 16 as encompassing a method for proliferating cardiomyocytes *in vivo* that, according to the Office Action, is directed to non-elected subject matter. Applicants have amended claim 1 to recite "*in vitro*" rendering the objection *moot*.

Information Disclosure Statement

Applicants appreciate the Examiner's consideration of the Information Disclosure Statement (IDS) filed on August 23, 2006. Applicants respectfully request that the Examiner also consider the IDS filed on June 5, 2006. For the Examiner's convenience, Applicant's attached the IDS filed on June 5, 2006 herewith as **Exhibit A**.

Rejections Under 35 U.S.C. § 103

Claims 1, 2, 4-8, 15-21 and 31 stand rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over Tamamori-Adachi et al. (Circ. Res. 92:e12-e19, 2003) (hereinafter "Adachi") in view of Poolman et al. (Circ. Res. 85: 117-127, 1999) (hereinafter "Poolman").

Applicants respectfully traverse this rejection.

The Office Action states that Adachi teaches a method for proliferating cardiomyocytes *in vitro* comprising introducing a cyclin and a cyclin-dependent kinase (CDK) using an adenovirus, wherein the cyclin is linked to nuclear localization signal. O.A. at page 4. The

Office Action concedes that Adachi "differs from the claimed invention by not teaching the introduction of a gene encoding a factor that inhibits the production or function of Cip/Kip family proteins into cardiomyocyte cultures." *Id.* at page 5.

Applicants agree that Adachi does not teach the introduction of a gene encoding a factor that inhibits the production, function or action of Cip/Kip family protein into cardiomyocytes. Indeed, Adachi does not teach or suggest the involvement of the Cip/Kip family protein (e.g., $p27^{Kip1}$) in the proliferation process of cardiomyocytes. Rather, as discussed in the specification, Adachi discloses a novel method of proliferating cardiomyocytes comprising the expression of a cyclin and a CDK. *See, e.g.*, page 3, line 13 to page 4, line 18.

The claimed invention is an improvement over the methods of Adachi. Indeed, when investigating the mechanism of the cell cycle regulation in cardiomyocytes, the inventors unexpectedly discovered that, *inter alia*, one of the Cip/Kip family proteins, the $p27^{Kip1}$ protein, was excessively accumulated in the nucleus of cardiomyocytes under stimulation with cyclin and CDK. *See, e.g.,* page 15, lines 8-12 and page 70, lines 7-9. The inventors further experimented by testing the effect of the Skp2 gene on the expression of the $p27^{Kip1}$ protein via the co-expression of the Skp2 gene in cardiomyocytes transfected with D1NLS and CDK4 genes. *See, e.g.*, Example 3. The co-expression of D1NLS, CDK4 and Skp2 genes resulted in a significant reduction of the $p27^{Kip1}$ protein. *See, e.g.*, page 77, lines 14-16 and Figures 6 and 7. The inventors then demonstrated that the co-expression of D1NLS, CDK4 and Skp2 gene significantly promoted the proliferation of cardiomyocytes. *See e.g.*, Example 4 and Figure 8 (showing that "cell number of cardiomyocytes with the three genes namely D1NLS, CDK4 and Skp2 genes expressed therein was increased 5 fold or more," as compared to cardiomyocytes infected with a control vector and cardiomyocytes infected with Ad-Skp2 alone) Accordingly, Applicants submit that the claimed method provides a novel and non-obvious method of proliferating cardiomyocytes.

The Office Action states that Poolman teaches the loss of the $p27^{Kip1}$ gene results in the proliferation of cardiac myocytes. O.A. at page 5. The Office Action asserts that Poolman therefore provides sufficient motivation for one of ordinary skill to introduce a gene encoding a factor that inhibits the production or function of the $p27^{Kip1}$ to the cardiomyocyte system of Adachi. *Id.*

Applicants respectfully disagree. As an initial matter, Applicants submit that Poolman does not directly prove the increase in the number of cardiomyocytes is due to the loss of the $p27^{Kip1}$ protein. At best, Poolman discloses that the loss of the $p27^{Kip1}$ gene in neonatal mice results in such an increase. The loss of the $p27^{Kip1}$ gene alone, however, is not sufficient for the efficient proliferation of cardiomyocytes. Indeed, the specification demonstrates that almost no increase in the cell number of cardiomyocytes was observed where the production of $p27^{Kip1}$ gene product was inhibited by infection with p27 siRNA alone. *See* Example 5 and Figures 9 and 10; *see also* page 82, lines 8-11 ("Almost no increase of the cell numbers of cardiomyocytes infected with ... Ad-p27 siRNA alone as negative controls was observed."). In contrast, the specification teaches that by the co-expression of D1NLS and CDK4, the inhibition of $p27^{Kip1}$ ($p27^{Kip1}$ siRNA infection) caused a significant increase of the cell number of cardiomyocytes. *See, e.g.*, Figure 10; *see also* page 82, lines 5-7 (" ... the cell number of cardiomyocytes with the three genes namely D1NLS, CDK4 and p27 siRNA genes expressed therein was significantly increased."). Accordingly, Poolman does not teach or suggest that introducing a gene encoding a factor that inhibits the production, function or action of Cip/Kip family protein promotes the proliferation of cardiomyocytes.

Applicants also submit that Poolman observes the effect of the loss of $p27^{Kip1}$ on the proliferation of cardiomyocytes only in postnatal mice, but not in adult mice. *See* Poolman at Figures 7-9. Indeed, the cardiomyocytes in adult mice have generally lost their growth activity. On the other hand, the claimed invention is applicable not only to neonatal cardiomyocytes, but also to adult cardiomyocytes. Furthermore, the specification discloses a therapeutic effect on damaged cardiomyocytes, i.e., the heart functions of the damaged animal model are maintained by the method of the invention. *See* Example 6, Figures 11-13 and Table 1 of the specification. These effects are neither taught nor suggested by Poolman.

Applicants further submit that Poolman fails to teach or suggest combining his $p27^{Kip1}$ gene silencing method with any other method, let alone with a method of co-expressing cyclins and/or CDKs. As such, Applicants submit that one of skill in the art would not have been motivated to use the method of Poolman with any method, let alone with the method of Adachi.

Applicants submit that Adachi, alone or in combination with Poolman, does not teach or suggest each and every claim limitation. Furthermore, Applicants submit that one of ordinary skill in the art would have no reason to combine the $p27^{Kip1}$ gene silencing method of Poolman

with the method of Adachi. Even assuming one of skill in the art had a reason to combine the teachings of Adachi and Poolman (and the combination taught each and every limitation), which Applicants do not concede, Applicants submit that the claimed invention provides unexpected results.

In view of the foregoing, Applicants respectfully request withdrawal of the rejection of Adachi in view of Poolman.[1]

Claims 9-12 and 22-25 stand rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over Adachi in view of Poolman, and in further view of Tsvetkov et al. (Curr. Bio. 9: 661-664, 1999) (hereinafter "Tsvetkov") and Yu et al. (PNAS 95: 11324-11329, 1998) (hereinafter "Yu").

Applicants respectfully traverse this rejection.

As discussed above, the combination of Adachi and Poolman do not teach or suggest the claimed invention.

Neither Tsvetkov nor Yu remedy the deficiencies of the combination of Adachi and Poolman. Indeed, neither Tsvetkov nor Yu teach or suggest a method of introducing a cyclin, a CDK and a gene encoding a factor that inhibits the production, function or action of Cip/Kip family protein into cardiomyocytes. Accordingly, Applicants submit the combination of Adachi and Poolman in view of Tsvetkov and/or Yu does not teach or suggest the claimed invention.

In view of the foregoing, Applicants respectfully request withdrawal of the rejection of Adachi in view of Poolman, and in further view of Tsvetkov and Yu.

Double Patenting

Claims 1, 2, 4-7, 16-21 and 31 stand rejected on the ground of nonstatutory obviousness-type double patenting as allegedly being unpatentable over claims 1, 2, 4, 18 and 19 of Application No. 10/713,008 ("the '008 application").[2]

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[1] Applicants note that the Office Action rejected claims 17-21 over Adachi in view Poolman. These claims are directed to vectors comprising a cyclin gene, a CDK gene and a gene encoding a factor that inhibits the production, function or action of Cip/Kip family protein. The Office Action, however, does not provide any reason why the combination of Adachi and Poolman teaches or suggests such vectors. Accordingly, Applicants respectfully request withdrawal of the rejection over claims 17-21.

Applicants respectfully submit that the instant claims cannot be rejected under this section as the '008 application is not a patent. Nonetheless, Applicants submit that the claimed invention is an improvement over the '008 application for the reasons discussed above with respect to Adachi. Indeed, Applicants submit the co-expression of a cyclin, CDK and gene encoding a factor that inhibits the production, function or action of Cip/Kip family protein provides a novel and non-obvious method of proliferating cardiomyocytes. Accordingly, Applicants respectfully request withdrawal of the double patenting rejection.

Rejections Under 35 U.S.C. § 112, Second Paragraph

Claims 4, 11 and 18 stand rejected over the recitation of "capable."

Applicants have amended claims 4, 11 and 18 to delete the recitation of "capable." Accordingly, Applicants respectfully submit the rejection under 35 U.S.C. § 112, second paragraph is *moot*.

[2] The Office Action refers to "U.S. Patent No. 10/713,008" and rejects the claims under nonstatutory obviousness-type double patenting. This appears to be a typographical error as 10/713,008 is an application.

CONCLUSION

Applicants respectfully submit that claims are in condition for allowance, and such disposition is earnestly solicited. Should the Examiner believe that any issues remain after consideration of this response, the Examiner encouraged to contact the Applicant's undersigned representative to discuss and resolve such issues.

It is believed that no additional fees are necessary for the submission of this response. However, should the USPTO determine that any additional fees are due in connection with this response, the Commissioner is hereby authorized to charge such fees to the undersigned's **Deposit Account No. 50-0206**.

Respectfully submitted,

HUNTON & WILLIAMS LLP

Date: November 13, 2007

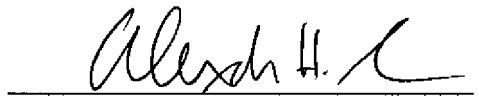
By: 

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Exhibit A

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Application Number	: TBA 10 580 248	Confirmation No.: TBA
Applicant	: Mimi ADACHI et al.	
International Filing Date	: November 19, 2004	
Title	: METHOD FOR PROLIFERATING CARDIOMYOCYTES	
TC/Art Unit	: TBA	
Examiner:	: TBA	
Docket No.	: 64517.000003	
Customer No.	: **21967**	

MAIL STOP PCT
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

INFORMATION DISCLOSURE STATEMENT

Sir:

In accordance with 37 C.F.R. §§ 1.97 and 1.98, and in compliance with the duty of disclosure set forth in 37 C.F.R. § 1.56, Applicants submit the attached Form PTO-SB/08A (modified) for consideration and request the references cited therein be made of record by the U.S. Patent and Trademark Office in the above-captioned application.

Several of the references listed on the attached Form PTO-SB/08A were cited by the Japanese Patent Office in the International Search Report and the Written Opinion of the International Searching Authority for International Application No. PCT/JP2004/017274.

Applicants respectfully point out that the submission of the listed references in this Information Disclosure Statement is not an admission that they are prior art or that they are material to patentability of any claims of the application. Also, the submission of this Information Disclosure Statement is not an indication that a search has been made by Applicants.

For the convenience of the Examiner in considering the cited references, a copy of each of the cited references is enclosed with this communication. In considering the cited references, it may be noted by the Examiner that certain of the references may contain markings, underlinings, and/or other notations. These markings, underlinings, and/or other notations are not to be construed as drawing the Examiner's attention either to selected parts or away from other parts of the cited references. Any such markings were either present on the copies of the cited

references obtained by the associated individuals, or were made thereon during the study of the references by the associated individuals.

As this application was filed after June 30, 2003, copies of U.S. patents and/or U.S. patent application publications for national stage applications under 35 U.S.C. 371 cited on the attached Form PTO-SB/08A (modified), are not being provided as specified in 1276 *O.G.* 55 (5 August 2003).

Consideration of the foregoing plus the prompt return of a copy of the enclosed Form SB/08B with the Examiner's initials in the left column in accordance with MPEP 609 are respectfully requested.

In accordance with 37 C.F.R. § 1.97(b), this Information Disclosure Statement is believed to be submitted prior to issuance of a first Office Action. Therefore, it is respectfully submitted that no fee is required for consideration of this information. However, in the event any fee is deemed necessary, the Commissioner is authorized to charge the undersigned's Deposit Account No. 50-0206.

Respectfully submitted,
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Dated: June 5, 2006

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